

REMARKS

Claims 1, 3, 5, 8-12, 17-24, 28, 57 and 58 are pending in this application. Claims 11, 12 and 22 have been amended to use proper Markush terminology. Claim 28 has been amended for purposes of clarity. New claim 59 has been added and includes subject matter removed from claim 22. New claim 60 has been added and included subject matter removed from claim 28. No new matter has been added.

1. Sequence Rules

The Examiner has indicated that the application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). The Examiner states that the application fails to comply with the requirements of 37 CFR 1.821 to 1.825 because the application discloses nucleotide sequences on p. 43, lines 8-9. Applicant respectfully disagrees with the Examiner's objection. Although p. 43 of the Specification does disclose two nucleotide sequences, Applicant submits that the sequence rules do not require Applicant to include these sequences in their sequence listing. Referring to MPEP 2422.01, Applicant would point out that the nucleotide and/or amino acid sequences as used in 37 CFR 1.821 to 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. In the instant case, the two nucleotide sequences found on p. 43 of the Specification only contain eight (8) nucleotides and, therefore, would not be encompassed by the rules. Accordingly, Applicant has not submitted a substitute Sequence Listing. Reconsideration and removal of the objection is respectfully requested.

2. Claim Objections

The Examiner has objected to claims 11, 12 and 22 because the claims do not use proper Markush terminology. The Examiner has indicated that the phrasing is awkward and may lead to confusion and requests correction. Applicant has made the appropriate correction. Claim 28 was objected to for a grammatical error. Applicant has amended the claim for purposes of clarity

and believes that the amendment has addressed the Examiner's concern. Reconsideration and removal of the objections are respectfully requested.

3. Obvious-type Non-Statutory Double Patenting

Claims 1, 3, 5, 8-12, 17-24, 57 and 58 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,645,500. Without conceding the propriety of the rejection, Applicant respectfully requests that the obvious-type non-statutory double patenting rejection be held in abeyance until the pending claims are allowed and/or a notice of allowance is issued in the present case.

4. Rejections under 35 U.S.C. §112, first paragraph

A. Enablement

The Examiner has rejected claims 1, 3, 5, 8-12, 17-24, 57 and 58 under 35 USC §112, first paragraph, because the Specification, while being enabling for a method for in vivo downregulation of osteoprotegerin ligand (OPGL) activity in an animal, the method comprising effecting presentation to the animal's immune system of an immunologically effective amount of at least one modified OPGL polypeptide thereof which has as a result that immunization of the animal with the modified OPGL polypeptide thereof induces production of antibodies against the animal's own OPGL polypeptide which down-regulates the animal's own OPGL activity, wherein said OPGL polypeptide thereof comprises the SEQ ID NO: 2 wherein at least one B-cell epitope is introduced in said sequence in residues 159-317, does not reasonable provide enablement for other permutations of the claimed formula, substitutions, mutations, insertions, deletions and alterations of the amino acid of SEQ ID NO: 2. (emphasis added). The Examiner concludes that the Specification does not enable a person of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claims. Applicant respectfully traverses.

The Examiner's principal argument that the claimed invention is not enabled is because the claims are drawn very broadly to methods of a vast number of B-cell epitope and OPGL

moiety combinations, yet the Specification fails to provide any guidance for the successful synthesis, isolation, and characterization of OPGL polypeptides, beyond the full-length OPGL and OPGL fragments consisting of residues 128-316, 137-316 and 158-316. The Examiner further states that an undue quantity of experimentation would be required to practice the invention due to the various complications in regards to targeting the effect of mutations in a protein, the immunological effect of mutation and the effects of the mutated polypeptide in an animal. Finally, the Examiner contends that the person of ordinary skill in the art would not recognize the efficacy of using the claimed OPGL-B-cell moieties *in vivo* based solely on its indirect evidence. In support of his position that the disclosure is not enabling, the Examiner cites to Applicant's statement on page 7, lines 3-4 of the Specification which states that "The *in vivo* evidence is partially circumstantial or indirect but it is our opinion . . .

First, Applicant would point out the level of skill in this particular art is particularly high and that this must be taken into account to determine whether an application is enabled or whether an invention is adequately described or supported. Peptide and polypeptide vaccination against self-proteins is well known in the art of immunology; antibodies raised against the self-protein will lead to its destruction or interfere with its function and hence result in down-regulation. The question to be answered is whether a person of ordinary skill in the art would reasonably believe that administering the claimed modified OPGL polypeptides would produce the intended result based on the teachings of the Specification. Contrary to the Examiner's statement, the inventors' belief in the claimed method was not solely based *indirect* evidence. As noted on in the first two paragraphs on page 7, it is evident that the inventors were also relying on direct evidence and were able to make reasoned conclusions about the role of OPGL. Applicant, therefore, submits that the skilled artisan could reasonably conclude and would expect that immunization with the claimed constructs would lead to the down regulation of OPGL activity in the animal based on the teachings in the Specification and their own knowledge regarding the use of peptide-based vaccines.

In paragraph 16 of the Office Action, the Examiner admits that it is entirely possible to use the claimed OPGL polypeptides in a method of immunization to reduce serum OPGL. However, the Examiner appears to take issue with the fact that the claims are broadly drawn to

methods of a “vast” number of B-cell epitope and OPGL moiety combinations. The Examiner further argues that the Specification fails to provide any guidance for the successful synthesis, isolation and characterization of these modified OPGL polypeptides (see paragraph 17) and further argues that the Specification lacks any “concrete guidance on the structure and position of B-cell or T-cell epitope placement in OPGL” which would ensure the appropriate immune response. (see paragraph 21). Thus, in the Examiner’s opinion, undue experimentation would be required to practice the full scope of the claimed invention.

Applicant strongly disagrees with the Examiner’s characterization that the Specification provides no concrete guidance respect to the placement of B-cell and T-cell epitopes. As mentioned above, the idea underlying the present invention rests on the realization that active vaccination against OPGL is a feasible and viable approach in the treatment of diseases characterized by excess bone loss. The claimed invention is directed to a polypeptide, which includes at least one preserved OPGL B-cell epitope. The modified OPGL polypeptide has a defined structure and formula as set forth in claim 1. Constructs falling within the defined formula will possess the desired immunogenicity. While it is true that the claim encompasses many modified OPGL constructs, immunogens not meeting the limitations set forth in claim 1 would be excluded from the scope of the claim. The Specification on pages 17 to 29 provides considerable guidance as to how construct modified OPGL polypeptides according to the claims. This detailed and lengthy discussion includes about every known technology for rendering self-proteins immunogenic. The Examiner’s attention is specifically directed to pages 18-20 which discusses several different approaches to producing modified OPGL polypeptides that maintain a substantial fraction of B-cell epitopes. The subsequent pages discuss the many techniques that can be used to introduce a foreign T-helper cell epitope. Depending on epitope chosen, the skilled artisan would be able to select the appropriate technique. Applicant, therefore, submits that the Specification explicitly teaches how to prepare these antigenic polypeptides and use them to down-regulate OPGL activity in an animal. Moreover, Applicant submits that the skilled artisan would recognize the methods of preparing and selecting suitable modified OPGL polypeptides, falling within the scope of the claims, using routine, art-recognized techniques to produce useful variants to practice the invention.

Applicant would emphasize that the fact that experimentation might be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983). "The test is not merely quantitative, since a considerable amount of experimentation is permitted, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). In the present case, Applicant submits that the Specification provides the requisite guidance. Applicant's position is further supported by the Rule 1.312 Declaration signed by Marc Herz of Pharmexa A/S, which was previously submitted in this case, which presents the results of experiments illustrating the effectiveness of the claimed modified OPGLs in eliciting the desired immune response. The Declaration of Dr. Herz demonstrates that the Specification teaches how to make and use the full scope of the invention. Dr. Herz was able to create human and murine OPGL constructs (i.e. peptide-based vaccines) and test the vaccines in a series of vaccination experiments and animal models of pathological bone disease. In Dr. Herz's opinion, the Specification describes how to make the peptide-based vaccines and the techniques used to create these constructs were well within the knowledge of a person skilled in the art. Similarly, Dr. Herz believes that vaccine design parameters and proper administration guidelines were also within the knowledge of a skilled artisan and generally described in the Specification. Dr. Herz's results clearly demonstrate that the peptide-based vaccines and the method of active vaccination against OPGL described in the application have been realized. Factual affidavits are evidence that must be considered (MPEP 2164.05). Applicant respectfully submits that the Specification teaches a person skilled in the art how to make and use the full scope of the claimed invention. In view of the foregoing remarks, reconsideration and removal of the rejections are respectfully requested.

B. Written Description

The Examiner has also rejected the claims as containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner argues that the claims are directed to B-cell epitopes containing

subsequences of OPGL with various changes but that does not require the entity to possess any conserved structure or other distinguishing feature. Thus, the Examiner argues that Applicant is not entitled to the genus of "agents that is defined by a myriad of possible B-cell/OPGL combinations". Applicant respectfully disagrees.

First, it is important to note each case involving the issue of written description must be decided on its own facts and that the precedential value of cases in the area of written description is extremely limited. Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555 (Fed. Cir. 1991). Secondly, it is important to recognize that this inquiry is conducted from the perspective of the skilled artisan. Contrary to the Examiner's opinion, Applicant submits that the skilled artisan, after reading the Specification, would recognize that the inventors had provided sufficient written description to evidence possession of the claimed genus --- modified OPGL polypeptides having preserved B-cell epitopes.

Second, Applicant would point out that the holding in Rochester is not applicable to the present situation. Unlike Rochester where the inventors did not generally or otherwise describe even a single compound to be used in the claimed method, the present inventors have discussed and provided examples of compounds which would fall within the claimed genus. The constructs encompassed by the present claims are not merely "as-yet-to-be-discovered" or hypothetical compounds. Nor, are they compounds whose activity has yet to be verified or confirmed. This is simply not a case where the method cannot be practiced until a compound is discovered that achieves the desired result. The present inventors have described and successfully used constructs according to the invention which exhibit the desired functionality. As Applicant has previously noted in their Supplemental Response filed on November 10, 2003, the constructs used in the experiments conducted by Dr. Hertz fell within the scope of the "modified OPGL polypeptides" recited in the claims.

Applicants are not required to provide a comprehensive list of each and every member of a claimed genus. An Applicant is entitled to a genus claim if they have described or exemplified a representative number of species. The disclosure of even a single species can adequately support a genus. (See MPEP 2163). The test is whether the skilled artisan would recognize that the Applicant was in possession of the necessary common attributes or feature of the elements

possessed by the members of the genus in view of the species disclosed or claimed. As discussed above, the members of the claimed genus are those constructs satisfying the requirements of claim 1. The Examiner argues that Applicant has not disclosed the complete or partial structure, physical and/or chemical properties, functional characteristics, etc. shared among members of the genus. The Examiner further states that the specification does not identify any particular portion of the structure that must be conserved. As discussed above, the claimed immunogenic constructs must contain at least one epitope (a preserved OPGL B-cell epitope). The Specification teaches that maintaining a substantial fraction of the original B-cell epitopes in OPGL is important in eliciting the desired immune response. Although it would be preferable to preserve the overall structure of the OPGL peptide, it is not required. The purpose of the invention is not to prepare active OPGL polypeptides. Rather, the purpose of the invention is to prepare modified OPGL polypeptides according to formula I which can be administered to an animal to induce an immune response whereby OPGL activity is down-regulated. Applicant submits that the skilled artisan, after reading the Specification, would be readily be able to identify members of the claimed genus. Thus, claims 1, 3, 5, 8-12, 17-24, 57 and 58 should be found to comply with the written description requirement and reconsideration and removal of the rejection is respectfully requested.

Favorable consideration and early allowance of the claims is earnestly solicited.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson (Reg. No. 30,330) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a three (3) month extension of time for filing a reply in connection with the present application, and the required fee of \$980.00 is to be charged to Deposit Account No. 02-2448.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Oct. 29, 2004
(Signature)

(Date of Signature)